Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-20 are pending in the application, with claim 1 being the independent claim. Claims 1 is sought to be amended to make explicit that which was implicit in the original claim. Support for this amendment may be found, for example, at page 5, paragraph [0015], lines 13-14. This change is believed to introduce no new matter, and its entry is respectfully requested.

Based on the above amendments and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Summary of the Office Action

In the Office Action dated December 2, 2002, there are ten rejections of the claims. Applicant respectfully offers the following remarks to overcome or traverse each of these rejections in the Office Action.

II. Rejections under 35 U.S.C. § 102

In the Office Action at pages 2-3, claims 1-3, 8, 11-12 and 14-18 are rejected under 35 U.S.C. § 102(b) over a variety of references. Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). The claims are not anticipated because the cited references neither expressly nor inherently disclose preparation of *latent* antithrombin III from *native* antithrombin III. Nothing in the Office Action establishes that latent antithrombin III was necessarily produced in any of the cited methods, and that it would have been recognized as such by a person skilled in the art. To be inherently disclosed, "the missing descriptive matter must necessarily be present in

the [cited reference] such that one skilled in the art would recognize such a disclosure." *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998). Finally, none of the cited references disclose the combination of *native* antithrombin III, sulfate ions and a Good's zwitterionic buffer other than Tris buffer. Additionally, none of the cited references expressly or inherently discloses the isolation of latent antithrombin III from the solution as recited in claim 17. For these reasons as well as the reasons presented below, Applicant respectfully requests that all of the rejections under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

A. The Rejection Under 35 U.S.C. § 102(b) Over Miller-Andersson et al.

Claims 1, 2, 17 and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Miller-Andersson *et al.* Applicant respectfully traverses this rejection.

Miller-Andersson *et al.* is alleged to disclose, in the abstract and at pages 442 and 447, purification of antithrombin III using affinity chromatography and using ammonium persulfate ($(NH_4)_2S_2O_8$). *See* Office Action, page 2. The abstract discloses purification of human antithrombin III using affinity chromatography on a heparin-Sepharose gel. Antithrombin III is an α_2-globulin. *See* page 446, lines 4-5. The disclosure of ammonium persulfate at page 442 relates to the use of ammonium persulfate as a catalyst for the polymerization (formation) of a polyacrylamide gel prior to gel electrophoresis. *See* page 442, lines 17-20. The polyacrylamide gel electrophoresis was conducted in the presence of a Tris-HCl buffer. *See* page 448, lines 1-3.

The claims are not anticipated by Miller-Andersson *et al.* The claims are directed to a process for the preparation of *latent* antithrombin III. Miller-Andersson *et al.* does not expressly or inherently disclose a process for the preparation of *latent* antithrombin III. Nothing in the Office Action even purports to support the notion that *latent* antithrombin III was produced by the cited method. Additionally, the Miller-Andersson reference relates to *per*sulfate ($S_2O_8^{2-}$), which is distinct from *sulfate* ions (SO_4^{2-}). (See, e.g., the enclosed Appendix A, which includes Material Safety Data Sheets (MSDS) for ammonium persulfate and ammonium sulfate). Moreover, the present claims exclude the use of Tris buffers. As disclosed in the specification, use of a TRIS buffer is not suitable for the presently claimed method. *See* paragraph [0015], lines 13-14. Miller-

Andersson *et al.* disclose the use of a Tris-HCl buffer composition when using the polyacrylamide gel that was polymerized using ammonium persulfate. Miller-Andersson *et al.* does not disclose the combination of native antithrombin III, *sulfate* ions and a Good's zwitterionic buffer other than Tris for the preparation of *latent* antithrombin III. Therefore, Miller-Andersson *et al.* does not anticipate the present claims.

In view of the foregoing amendments and remarks, Applicant respectfully requests that the rejection under 35 U.S.C. § 102(b) over Miller-Andersson *et al.* be reconsidered and withdrawn.

B. The Rejection Under 35 U.S.C. § 102(b) Over Schwinn et al. U.S. Patent No. 4,405,603, Schwinn et al. U.S. Patent No. 4,411,794, or Schwinn et al. U.S. Patent No. 4,404,187.

Claims 1-3, 11, 12 and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Schwinn *et al.*, U.S. Patent No. 4,405,603 (hereinafter "'603"), Schwinn *et al.*, U.S. Patent No. 4,411,794 (hereinafter "'794") or Schwinn *et al.*, U.S. Patent No. 4,404,187 (hereinafter "'187"). Applicant respectfully traverses this rejection.

Schwinn *et al.*, '603 is alleged to disclose, in example 1, antithrombin III incubated with ammonium sulfate at a pH of 8.0. *See* Office Action, page 2. Example 1 discloses a method for the preparation of a hepatitis-safe concentrate of Factors IX/X from human citrate plasma. Column 4, lines 21-22. The adsorbent, i.e. the material comprising Factors IX or X, is mixed with ammonium sulfate and then washed with 20L of a 0.5 M NaCl solution. Column 4, lines 35 and 39-41. The washed adsorbant is eluted with a buffer comprising 0.3 U/ml of antithrombin III. Column 4, lines 41-45. This eluent is mixed with colloidal silica and the resulting eluate is separated from the adsorbent by centrifugation. Column 4, lines 45-48. Finally, the supernatant liquid is dialyzed against a buffer containing NaCl, trisodium citrate and glycine. Column 4, lines 48-51.

The claims are not anticipated by Schwinn *et al.*, '603. The claims are directed to a process for the preparation of *latent* antithrombin III. First, Schwinn *et al.*, '603 does not expressly or inherently disclose a process for the preparation of *latent* antithrombin III for the reasons stated in Section II above. Second, Schwinn *et al.*, '603 disclose that the

ammonium sulfate containing composition was washed with 20L of a NaCl solution prior to addition of antithrombin III, which is not disclosed to be *native* antithrombin III. Nothing in the Office Action establishes that, after washing with 20L of a NaCl solution, any sulfate ions remained in the composition *prior to* the addition of antithrombin III. Third, the present claims require the use of a Good's zwitterionic buffer other than Tris. Schwinn *et al.*, '603 does not disclose the use of *any* Good's zwitterionic buffer in combination with antithrombin III and sulfate ions. In summary, Schwinn *et al.*, '603 does not disclose the combination of native antithrombin III, sulfate ions and a Good's zwitterionic buffer for the preparation of *latent* antithrombin III. Therefore, Schwinn *et al.*, '603 does not anticipate the present claims.

Schwinn *et al.*, '794 is alleged to disclose, in example 1, antithrombin III incubated with ammonium sulfate at a pH of 8.0. *See* Office Action, page 2. Example 1 discloses a method for the preparation of a concentrate of Factors II, VI, IX and X from human plasma. Column 3, lines 44-45. The plasma solution is mixed with ammonium sulfate. Column 3, line 51. After centrifugation, sulfate ions are removed by dialysis. Column 4, lines 1-2. The adsorbent, comprising Factors II, VI, IX and X, is then eluted using a buffer solution comprising 0.3 U/ml of antithrombin III. Column 4, lines 9-12.

The claims are not anticipated by Schwinn *et al.*, '794. First, Schwinn *et al.*, '794 does not expressly or inherently disclose a process for the preparation of *latent* antithrombin III for the reasons stated in Section II above. Second, Schwinn *et al.*, '794 does not disclose incubation of *native* antithrombin III with sulfate ions; sulfate ions were *removed* by dialysis *prior to* the addition of 0.3 U/ml of antithrombin III, which is not disclosed to be *native* antithrombin III. Column 4, lines 1-2. Third, Schwinn *et al.*, '794 does not disclose the use of *any* Good's zwitterionic buffer in combination with antithrombin III and sulfate ions. In summary, Schwinn *et al.*, '794 does not disclose the combination of native antithrombin III, sulfate ions and a Good's zwitterionic buffer for the preparation of *latent* antithrombin III. Therefore, Schwinn *et al.*, '794 does not anticipate the claims.

Schwinn *et al.*, '187 is alleged to disclose, in example 1, antithrombin III incubated with ammonium sulfate at a pH of 8.0. *See* Office Action, page 2. Example 1 discloses a method for the preparation of a hepatitis-safe concentrate of Factors II/VII

from human citrate plasma. Column 4, lines 42-43. The eluate-citrate plasma mixture is admixed with ammonium sulfate, centrifuged and then washed twice with 20L of 0.5 M NaCl. Column 4, lines 55-57 and 60-62. The adsorbent is then eluted using a buffer solution comprising 0.3 U/ml of antithrombin III. Column 4, lines 62-66.

The claims are not anticipated by Schwinn *et al.*, '187. First, Schwinn *et al.*, '187 does not expressly or inherently disclose a process for the preparation of *latent* antithrombin III for the reasons stated in Section II above. Second, as noted above, nothing in the Office Action establishes that, following centrifugation and washing with 20L of a NaCl solution, any sulfate ions remained in the composition *prior to* the addition of antithrombin III. Third, Schwinn *et al.*, '187 does not disclose the use of *any* Good's zwitterionic buffer. In summary, Schwinn *et al.*, '187 does not disclose the combination of native antithrombin III, sulfate ions and a Good's zwitterionic buffer for the preparation of *latent* antithrombin III. Therefore, Schwinn *et al.*, '187 does not anticipate the claims.

In view of the foregoing amendments and remarks, Applicant respectfully requests that the rejections under 35 U.S.C. § 102(b) over Schwinn *et al.* ('603, '794 and '187) be reconsidered and withdrawn.

C. The Rejection Under 35 U.S.C. § 102(b) Over Eibl et al. U.S. Patent No. 4,388,232.

Claims 1-3 and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Eibl *et al.*, U.S. Patent No. 4,338,232 (hereinafter "'232"). Applicant respectfully traverses this rejection.

Eibl *et al.*, '232, is alleged to disclose, in examples 9 and 11, antithrombin III incubated with ammonium sulfate. *See* Office Action, pages 2 and 3. Example 9 discloses the purification of immune globulin fraction. Column 9, line 56. An immune globulin paste, in the presence of 300 units of antithrombin III and 600 units of heparin, was dialyzed and thereafter precipitated with ammonium sulfate to produce a purified immune globulin fraction. Column 10, lines 7-15. Example 11 discloses the preparation of a C1-esterase inhibitor. Column 10, line 47. A DEAE-Sephadex column eluted C1-esterase inhibitor was precipitated with polyethylene glycol and dissolved in a solution comprising 1,250 units of antithrombin III and then precipitated with ammonium sulfate

to produce a purified C1-esterase inhibitor. Column 10, lines 56-68.

The claims are not anticipated by Eibl *et al.*, '232. First, Eibl *et al.*, '232 does not disclose a process for the preparation of *latent* antithrombin III for the reasons stated in Section II above. Further, neither example 9 nor example 11 disclose antithrombin III to be *native* antithrombin III and nothing in the Office Action establishes that *latent* antithrombin III is produced at the end of either process. Second, Eibl *et al.*, '232 does not disclose the use of *any* Good's zwitterionic buffer. Eibl *et al.*, '232 only discloses use of a saline solution during these steps. Column 10, lines 8, 15, 60-61 and 68. In summary, Eibl *et al.*, '232 does not disclose the combination of *native* antithrombin III, sulfate ions and a Good's zwitterionic buffer other than Tris for the preparation of *latent* antithrombin III. Therefore, Eibl *et al.*, '232 does not anticipate the claims.

In view of the foregoing amendments and remarks, Applicant respectfully requests that the rejection under 35 U.S.C. § 102(b) over Eibl *et al.*, '232, be reconsidered and withdrawn.

D. The Rejection Under 35 U.S.C. § 102(b) Over Eibl et al. U.S. Patent No. 4,510,084.

Claims 1-3 and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Eibl *et al.* U.S. Patent No. 4,510,084 (hereinafter "'084"). Applicant respectfully traverses this rejection.

Eibl *et al.*, '084 is alleged to disclose, at column 3 and in the claims, incubation of antithrombin III in ammonium sulfate and use of heat to inactivate any viruses. *See* Office Action, page 3. Eibl *et al.* discloses a plasma heparin solution admixed with DEAE-Sephadex A 50. Column 3, lines 12-16. This mixture was washed with a phophate-citrate [sic] buffered, isotonic saline solution having a pH of 7.5. Column 3, lines 16-19. After further incubation in a phophate [sic] citrate buffered saline solution, the eluates were combined with ammonium sulfate at a pH of 5.5. Column 3, lines 26-28. An additional ammonium sulfate step is disclosed prior to a final dialysis step. Column 3, lines 40-45.

The claims are not anticipated by Eibl *et al.*, '084. First, Eibl *et al.* '084 does not

expressly or inherently disclose a process for the preparation of *latent* antithrombin III for the reasons stated in Section II above. Eibl *et al.* '084 discloses a method for producing an antithrombin III-heparin complex. *See* Example 1. Eibl *et al.* '084 does not disclose a process for the preparation of *latent* antithrombin III. Second, Eibl *et al.* '084 does not disclose use of *any* Good's zwitterionic buffer. Rather, Eibl *et al.* '084 utilizes a phophate-citrate [sic] buffer system to contact antithrombin III. In summary, Eibl *et al.*, '084 does not disclose the combination of *native* antithrombin III, sulfate ions and a Good's zwitterionic buffer other than Tris for the preparation of *latent* antithrombin III. Therefore, Eibl *et al.*, '084 does not anticipate the claims.

In view of the foregoing amendments and remarks, Applicant respectfully requests that the rejection under 35 U.S.C. § 102(b) over Eibl *et al.*, '084, be reconsidered and withdrawn.

E. The Rejection Under 35 U.S.C. § 102(b) Over Schwinn et al. U.S. Patent No. 4,297,344.

Claims 1-3 and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Schwinn *et al.* U.S. Patent No. 4,297,344 (hereinafter "'344"). Applicant respectfully traverses this rejection.

Schwinn *et al.*, '344, is alleged to disclose incubation of antithrombin III in ammonium sulfate with TRIS buffer at a concentration of 2 mM and at a pH of 8.5. *See* Office Action, page 3. The plasma sample is fed through a small column equilibrated with 0.02M TRIS, 0.01M citrate and 0.15M NaCl, washed with buffer and eluted. Column 12, lines 59-62. Ammonium sulfate is added to the eluate. Column 12, lines 66-68.

The claims are not anticipated by Schwinn *et al.*, '344. First, Schwinn *et al.*, '344 does not expressly or inherently disclose a process for the preparation of *latent* antithrombin III for the reasons stated in Section II above. Second, Schwinn *et al.*, '344, discloses the use of a TRIS buffer to contact antithrombin III. Column 12, line 60. As stated in Section II(A) above, use of a TRIS buffer is not suitable for the presently claimed method. In summary, Schwinn *et al.*, '344 does not disclose the combination of

native antithrombin III, sulfate ions and a Good's zwitterionic buffer *other than Tris* for the preparation of *latent* antithrombin III. Therefore, Schwinn *et al.*, '344 does not anticipate the claims.

In view of the foregoing amendments and remarks, Applicant respectfully requests that the rejection under 35 U.S.C. § 102(b) over Schwinn *et al.*, '344, be reconsidered and withdrawn.

III. Rejections Under 35 U.S.C. § 103(a)

In the Office Action at pages 4-7, claims 1-20 are rejected under 35 U.S.C. § 103(a).

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). As will be discussed in detail below, the Examiner's burden has not been satisfied.

A. The Rejection Under 35 U.S.C. § 103(a) Over Miller-Andersson et al. In View of Cahalan et al., U.S. Patent No. 5,229,172, Cahalan et al., U.S. Patent No. 5,767,108, or JP11209399A, Good et al. and Schwinn et al., '344.

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Miller-Andersson *et al.* in view of Cahalan *et al.*, U.S. Patent No. 5,229,172 (hereinafter

"'172"), Cahalan *et al.*, U.S. Patent No. 5,767,108 (hereinafter "'108"), or JP 11209399A, Good *et al.* and Schwinn *et al.*, '344. Applicant respectfully traverses this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because the references, even when combined, do not result in the claimed invention and there would have been no motivation to combine the references. As stated in Section II(A) above, Miller-Andersson *et al.* does not disclose (1) a process for the preparation of *latent* antithrombin III, (2) the use of *sulfate* ions, or (3) the use of a Good's buffer other than Tris. As discussed above, the Miller-Andersson reference relates to the use of *per*sulfate ions, which are distinct from the sulfate ions used in the present invention. A person of ordinary skill in the art would not have been motivated to use ammonium *per*sulfate in a method for purifying a protein because ammonium persulfate is an oxidizing agent and thus would be expected to destroy the structure of the protein by oxidizing S-S bonds (see the enclosed MSDS for ammonium persulfate, which indicates that it is "oxidizing"). The secondary references, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Good *et al.* and Schwinn *et al.*, '344, do not cure the deficiencies in Miller-Andersson *et al.* and none of the references provide motivation to combine the relevant disclosures.

The Cahalan references and JP 11209399A merely disclose that antithrombin III is contacted with MES and HEPES buffers. There would have been no motivation to substitute MES or HEPES buffers for the Tris-HCl disclosed in Miller-Andersson *et al.* Cahalan *et al.*, '172, Cahalan *et al.*, '108 and JP 11209399A do not cure the deficiencies in Miller-Andersson *et al.*

Good *et al.* merely discloses a class of zwitterionic buffers. Good *et al.* does not disclose that these buffers should be used in a method for preparing *latent* antithrombin III from *native* antithrombin III. Nor does Good *et al.* disclose that Tris is an inappropriate buffer for the presently claimed invention. Thus, Good *et al.* does not cure the deficiencies in Miller-Andersson *et al.*

Schwinn *et al.*, '344 has the same deficiencies as Miller-Andersson *et al.* Schwinn *et al.*, '344, does not disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. *See* Section II(E) above. Schwinn *et al.*, '344 does not cure the deficiencies in Miller-Andersson *et al.* Further, there would have been no reason to combine two references which are equally deficient.

The Examiner has failed to establish a *prima facie* case of obviousness. There is no objective teaching in the prior art or a showing that the knowledge generally available to one of ordinary skill in the art would have led that individual to combine the relevant teachings of the references to arrive at the presently claimed invention. Nothing in the Office Action points to such a teaching. Further, even if there had been motivation to combine the references, the combination does not result in the presently claimed invention because the cited references, even in combination, fail to teach or suggest a method for preparing *latent* antithrombin III by using *sulfate* ions. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Miller-Andersson *et al.* in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Good *et al.* and Schwinn *et al.*, '344, be reconsidered and withdrawn.

B. The Rejection Under 35 U.S.C. § 103(a) Over Eibl et al., '232, In View of Cahalan et al., '172, Cahalan et al., '108, or JP 11209399A, Miller-Andersson et al., Good et al. and Schwinn et al., '344.

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Eibl *et al.*, '232, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, Good *et al.* and Schwinn *et al.*, '344. Applicant respectfully traverses this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because the references, even when combined, do not result in the claimed invention and there is no motivation to combine the references. As stated in Section II(C) above, Eibl *et al.*, '232, does not disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. The secondary references, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, Good *et al.* and Schwinn *et al.*, '344, do not cure the deficiencies in Eibl *et al.*, '232 and none of the references provide motivation to combine the relevant disclosures.

As discussed in Section II(C), the deficiencies in Eibl *et al.*, '232 are similar to those in Miller-Anderson *et al.*, which deficiencies have been addressed in Section III(A) above. Since Eibl *et al.*, '232 and Miller-Anderson *et al.* share the same deficiencies, there would have been no reason to combine two references which are equally deficient.

The disclosures of Cahalan *et al.*, '172, Cahalan *et al.*, '108, JP 11209399A, Good *et al.* and Scwhinn *et al.*, '344, their relationship to the present claims, and their failure to provide motivation to combine have been discussed in Section III(A) above. All the secondary references fail to disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris and therefore fail to cure the deficiencies in Eibl *et al.*, '232.

The Examiner has failed to establish a *prima facie* case of obviousness. There is no objective teaching in the prior art or a showing that the knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references to arrive at the presently claimed invention. Where in the art is it taught that latent antithrombin III can be prepared by incubating native antithrombin III with the combination of sulfate ions and a Good's buffer other than Tris? Further, even if there were motivation to combine the references, the combination does not result in the presently claimed invention because the cited references fail to suggest a method for preparing latent antithrombin III. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Eibl *et al.*, '232, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, Good *et al.* and Schwinn *et al.*, '344, be reconsidered and withdrawn.

C. The Rejection Under 35 U.S.C. § 103(a) Over Schwinn et al. '603, Schwinn et al. '794, or Schwinn et al. '187, In View of Eibl et al., '084 or Schwinn et al., '344, Cahalan et al., '172, Cahalan et al., '108, or JP 11209399A, Miller-Andersson et al., and Good et al.

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Schwinn *et al.*, '603, Schwinn *et al.*, '794 or Schwinn *et al.*, '187, in view of Eibl *et al.*, '084, or Schwinn *et al.*, '344, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, and Good *et al.* Applicant respectfully traverses this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because the references, when combined, do not result in the claimed invention and there would have been no motivation to combine the references. As stated in Section II(B) above, the Schwinn references ('603, '794 or '187) do not disclose (1) a process for the preparation of

latent antithrombin III and (2) the use of a Good's buffer other than Tris. The secondary references, Eibl *et al.*, '084 or Schwinn *et al.*, '344, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, and Good *et al.*, do not cure the deficiencies in the Schwinn references ('603, '794 or '187) and none of the references provide motivation to combine the relevant disclosures.

As discussed in Section II(B) above, the deficiencies in the Schwinn references ('603, '794 or '187) are similar to those in Miller-Anderson *et al.*, which deficiencies have been addressed in Section III(A) above. The disclosures of Cahalan *et al.*, '172, Cahalan *et al.*, '108, JP 11209399A, Good *et al.* and Scwhinn *et al.*, '344, their relationship to the present claims, and their failure to provide motivation to combine have been discussed in Section III(A) above. Eibl *et al.*, '084 also fails to disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. *See* Section II(D) above. Since the Schwinn references ('603, '794 or '187) share the same deficiencies with Eibl *et al.*, '084 and Miller-Anderson *et al.*, there would have been no reason to combine these references which are equally deficient. All the secondary references fail to disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris and therefore fail to cure the deficiencies in the Schwinn references ('603, '794 or '187).

The Examiner has failed to establish a *prima facie* case of obviousness. There is no objective teaching in the prior art or a showing that the knowledge generally available to one of ordinary skill in the art would have led that individual to combine the relevant teachings of the references to arrive at the presently claimed invention. Further, even if there was motivation to combine the references, the combination does not result in the presently claimed invention because the cited references fail to suggest a method for preparing latent antithrombin III. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Schwinn *et al.*, '603, Schwinn *et al.*, '794 or Schwinn *et al.*, '187, in view of Eibl *et al.*, '084, or Schwinn *et al.*, '344, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, and Good *et al.*

D. The Rejection Under 35 U.S.C. § 103(a) Over Eibl et al., '084, In View of Cahalan et al., '172, Cahalan et al., '108, or JP 11209399A, Miller-Andersson et al. and Good et al.

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Eibl *et al.*, '084, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.* Applicant respectfully traverses this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because the references, when combined, do not result in the claimed invention and there is no motivation to combine the references. As stated in Sections II(D) and III(C) above, Eibl *et al.*, '084, does not disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. The secondary references, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.* do not cure the deficiencies in Eibl *et al.*, '084 and none of the references provide motivation to combine the relevant disclosures.

As discussed in Section II(D) above, the deficiencies in Eibl *et al.*, '084 are similar to those in Miller-Anderson *et al.*; which deficiencies have been addressed in Section III(A) above. Since Eibl *et al.*, '084 and Miller-Anderson *et al.* share the same deficiencies, there is no reason to combine two references which are equally deficient. The disclosures of Cahalan *et al.*, '172, Cahalan *et al.*, '108, JP 11209399A, and Good *et al.*, their relationship to the present claims, and their failure to provide motivation to combine have been discussed in Section III(A) above. All the secondary references fail to disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris and therefore fail to cure the deficiencies in Eibl *et al.*, '084.

The Examiner has failed to establish a *prima facie* case of obviousness. There is no objective teaching in the prior art or a showing that the knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references to arrive at the presently claimed invention. Further, even if there was motivation to combine the references, the combination does not result in the presently claimed invention because the cited references fail to suggest a method for preparing latent antithrombin III. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Eibl *et al.*, '084, in view of Cahalan *et al.*, '172,

Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.*, be reconsidered and withdrawn.

E. The Rejection Under 35 U.S.C. § 103(a) Over Schwinn et al., '344, In View of Cahalan et al., '172, Cahalan et al., '108, or JP 11209399A, Miller-Andersson et al. and Good et al.

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Schwinn *et al.*, '084, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.* Applicant respectfully traverses this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because the references, when combined, do not result in the claimed invention and there is no motivation to combine the references. As stated in Sections II(E) and III(A) above, Schwinn *et al.*, '344, does not disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. The secondary references, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.* Miller-Andersson *et al.* do not cure the deficiencies in Schwinn *et al.*, '344 and none of the references provide motivation to combine the relevant disclosures.

As discussed in Section II(E) above, the deficiencies in Schwinn *et al.*, '344 are similar to those in Miller-Anderson *et al.*; which deficiencies have been addressed in Section III(A) above. Since Schwinn *et al.*, '344 and Miller-Anderson *et al.* share the same deficiencies, there would have been no reason to combine two references which are equally deficient. The disclosures of Cahalan *et al.*, '172, Cahalan *et al.*, '108, JP 11209399A, and Good *et al.*, their relationship to the present claims, and their failure to provide motivation to combine have been discussed in Section III(A) above. All the secondary references fail to disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris and therefore fail to cure the deficiencies in Schwinn *et al.*, '344.

The Examiner has failed to establish a *prima facie* case of obviousness. There is no objective teaching in the prior art or a showing that the knowledge generally available

to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references to arrive at the presently claimed invention. Further, even if there was motivation to combine the references, the combination does not result in the presently claimed invention because the cited references fail to suggest a method for preparing latent antithrombin III. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Schwinn *et al.*, '344, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.*, be reconsidered and withdrawn.

IV. Other Matters

Applicant wishes to thank the Examiner for mailing on February 27, 2003 copies of the references cited in PTO-form 892, which were relied upon for the rejections and which were originally omitted with the mailing of the Office Action on December 2, 2002.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Eldora Ellison Floyd
Attorney for Applicant
Registration No. 39,967

Date: May 2, 2003

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::ODMA\MHODMA\SKGF_DC1;112356;1

Safety (MSDS) data for ammonium sulfate

General

Synonyms: actamaster, ammonium sulphate, diammonium sulfate, diammonium sulphate, dolamin, mascagnite, sulfuric acid diammonium salt
Molecular formula: $(NH_4)_2SO_4$

CAS No: 7783-20-2
EC No: 231-984-1

Physical data

Appearance: white crystals, granules or powder
Melting point: ca. 280 C (decomposes)
Boiling point:
Vapour density:
Vapour pressure:
Density (g cm^{-3}): 1.77
Flash point:
Explosion limits:
Autoignition temperature:
Water solubility: appreciable

Stability

Stable. Contact with strong oxidizers may cause fire or explosion.

Incompatible with strong bases.

Toxicology

Harmful if swallowed. Eye, skin and respiratory irritant.

Toxicity data
(The meaning of any abbreviations which appear in this section is given here.)
ORL-RAT LD50 3000 mg kg^{-1}
IPR-MUS LD50 610 mg kg^{-1}
IPR-MUS LD50 610 mg kg^{-1}

Risk phrases
(The meaning of any risk phrases which appear in this section is given here.)
R20 R36 R37 R38.

Transport information

Non-hazardous for air, sea and road freight.

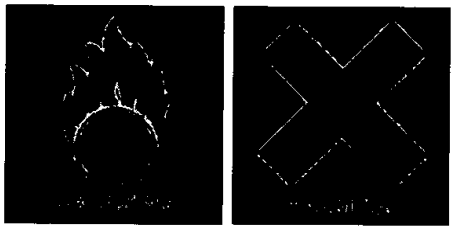
Personal protection

Safety glasses. Do not breathe dust.

Safety phrases
(The meaning of any safety phrases which appear in this section is given here.)
S26 S36.

[Return to Physical & Theoretical Chemistry Lab. Safety home page.]

Safety (MSDS) data for ammonium persulfate



General

Synonyms: ammonium persulphate, ammonium peroxodisulphate, diammonium persulfate, ammonium peroxydisulfate
Molecular formula: $H_8N_2O_8S_2$
CAS No: 7727-54-0
EC No: 231-786-5

Physical data

Appearance: colourless or white crystals
Melting point: 120 C
Boiling point:
Vapour density: 7.9 (air = 1)
Vapour pressure:
Specific gravity: 1.98
Flash point:
Explosion limits:
Autoignition temperature:

Stability

Stable. Oxidizing. May ignite combustible material. Incompatible with bases, combustible material, hydrogen peroxide, peroxy compounds, silver compounds, zinc. May decompose upon exposure to water or moist air.

Toxicology

Harmful if swallowed. Very destructive of mucous membranes. May cause dermatitis. May cause irritation. May cause sensitization.

Toxicity data
(The meaning of any abbreviations which appear in this section is given here.)
ORL-RAT LD50 689 mg kg^{-1}

Risk phrases
(The meaning of any risk phrases which appear in this section is given here.)
R8 R22 R34 R42 R43.

Transport information

(The meaning of any UN hazard codes which appear in this section is given here.)
UN Major hazard class: 5.1. Packing group: III

Personal protection

Safety glasses, adequate ventilation.

Safety phrases
(The meaning of any safety phrases which appear in this section is given here.)
S17 S22 S24 S36 S37 S39 S43.

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